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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, DC 20005

Telephone
(202) 408-4000

Facsimile
(202) 408-4400

FACSIMILE TRANSMITTAL

To: **Maher M. Haddad**

Firm: USPTO (Group Art Unit 1644)

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Subject: Atty. Doc. 08201.0024-00000 Date: October 30, 2003

From: Konstantin M. Linnik, Ph.d. Phone No.: 617.452.1626

Fax # Verified by: K. Bastarache No. of Pages (incl. this page) 5

Confirmation Copy to Follow: No

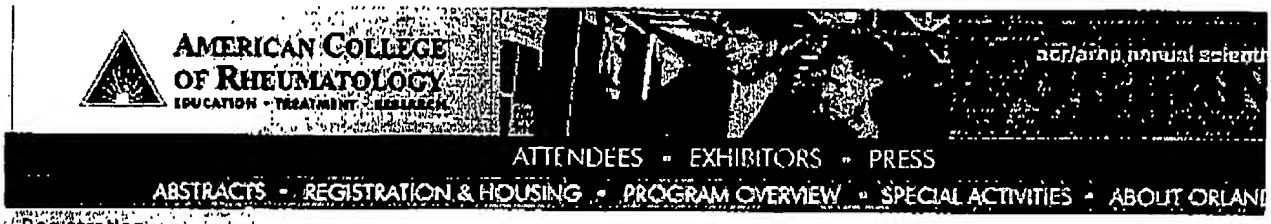
Message:

Dear Maher:

Thank you again for setting up the phone interview. I have attached two published abstracts, for your review, prior to the interview on November 6, 2003.

With best regards,

Konstantin



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2003 Abstracts

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Important Dates

October 23-24

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	Presentation	Authors	Session
1. ☐	922. Safety, Pharmacokinetic and Pharmacodynamic Results of a Phase 1 Single and Double Dose-Escalation Study of LymphoStat-B (Human Monoclonal Antibody to BLyS) in SLE Patients (Board 317)	R. Furie[1], W. Stohl[2], E. Ginzler[3], M. Becker[4], N. Mishra[5], W. Chatham[6], Joan T. Merrill[7], A. Weinstein[8], W. J. McCune[9], J. Zhong[10], W. Freimuth[10], and the LymphoStat-B Study Group. [1]North Shore Univ Hosp, Manhasset, NY; [2]USC, Los Angeles, CA; [3]SUNY Downstate, Brooklyn, NY; [4]U Chicago, Chicago, IL; [5]Wake Forest U, Winston-Salem, NC; [6]UAB, Birmingham, AL; [7]OMRF, Oklahoma City, OK; [8]Wash Hosp Ctr, Washington, DC; [9]U Michigan, Ann Arbor, MI; [10]Human Genome Sciences, Rockville, MD	**ACR/ARHP Poster Session B** SLE Treatment—Biologic Agents Sunday, 8:00 a.m. - 4:00 p.m. Convention Center - Hall D - E
2. ☐	1537. Effects of LymphoStat-B, a BLyS Antagonist, when Administered Intravenously to Cynomolgus Monkeys. (Board 380)	Wendy B. G. Halpern[1], Patrick Lappin[2], Thomas Zanardi[2], David M. Hilbert[1], Paul A. Moore[1], Vivian R. Albert[1], Kevin P. Baker[1]. [1]Human Genome Sciences Inc., Rockville, MD; [2]Charles River Laboratories, Sparks, NV	**ACR/ARHP Poster Session C** SLE—Animal Models II: B-Cells/Pathogenesis Monday, 8:00 a.m. - 4:00 p.m. Convention Center - Hall D - E

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Effects of LymphoStat-B, a BLyS Antagonist, when Administered Intravenously to Cynomolgus Monkeys.

Category: 26 SLE—animal models

Wendy B. G. Halpern[1], Patrick Lappin[2], Thomas Zanardi[2], David M. Hilbert[1], Paul A. Moore[1], Vivian R. Albert[1], Kevin P. Baker[1]. [1]Human Genome Sciences Inc., Rockville, MD; [2]Charles River Laboratories, Sparks, NV

Presentation Number: 1537

Poster Board Number: 380

Purpose: This study was conducted to evaluate the tolerability and effects of LymphoStat-B administered over 6 months to cynomolgus monkeys. LymphoStat-B is a fully-human IgG_1 lambda antibody directed against B-lymphocyte stimulator (BLyS). BLyS is a TNF family member that supports B-lymphocyte maturation and survival and has been implicated in the pathogenesis of several autoimmune diseases. LymphoStat-B was developed to antagonize the activity of BLyS in autoimmune disease, where undesirable effects of B-lymphocyte activity may cause or contribute to disease. LymphoStat-B binds specifically and with high affinity to recombinant BLyS protein from both humans and cynomolgus monkeys, and neutralizes their bioactivity *in vitro*.

Methods: LymphoStat-B was administered intravenously every other week to 16 monkeys per group at 5, 15 or 50 mg/kg/dose. A vehicle control was administered to 12 monkeys. Pharmacodynamic study endpoints included immunophenotyping of peripheral blood and tissues (spleen and lymph node), as well as standard clinical and anatomic pathology. Pathology endpoints were evaluated after 3 and 6 months of treatment, and after an 8-month treatment free (recovery) period.

Results: LymphoStat-B was well tolerated when administered intravenously to cynomolgus monkeys at doses up to 50 mg/kg for as long as 26 weeks, with no treatment-related infections identified. As detected by flow cytometric methods, monkeys exposed to LymphoStat-B had significant decreases in peripheral blood $CD20^+$ lymphocytes (B-cells) and $CD20^+/CD21^+$ lymphocytes (mature B-cells) after 13 weeks of exposure, with concomitant decreases in spleen and lymph node B-lymphocyte representation (both $CD20^+$ and $CD20^+/CD21^+$ cells). In contrast, neither $CD3^+$ T-lymphocytes nor $CD3^-/CD14^+$ monocytes were affected by LymphoStat-B. Microscopically, monkeys treated with LymphoStat-B had mild to marked decreases in the number and size of lymphoid follicles in the white pulp of the spleen. In addition, decreased spleen weights were evident after 26 weeks of exposure in LymphoStat-B treated monkeys. Overall there was a general correlation between peripheral blood B-lymphocytes, tissue B-lymphocyte representation, spleen weights and histologic findings. Total lymphocyte counts were similar in all groups throughout the study. In this study LymphoStat-B administration did not clearly affect globulins, albumin to globulin ratio, or immunoglobulin subclasses. All findings were generally reversible within the 8 month recovery period.

Conclusions: These data confirm the specific pharmacologic activity of LymphoStat-B in reducing B-lymphocytes in the cynomolgus monkey. Furthermore, the nonclinical safety profile of LymphoStat-B in monkeys supports its clinical development as a potential therapeutic for the treatment of autoimmune disease.

Safety, Pharmacokinetic and Pharmacodynamic Results of a Phase 1 Single and Double Dose-Escalation Study of LymphoStat-B (Human Monoclonal Antibody to BLyS) in SLE Patients

Category: 24 SLE—treatment: developments in the treatment of SLE

R. Furie[1], W. Stohl[2], E. Ginzler[3], M. Becker[4], N. Mishra[5], W. Chatham[6], Joan T. Merrill[7], A. Weinstein[8], W. J. McCune[9], J. Zhong[10], W. Freimuth[10], and the LymphoStat-B Study Group. [1]North Shore Univ Hosp, Manhasset, NY; [2]USC, Los Angeles, CA; [3]SUNY Downstate, Brooklyn, NY; [4]U Chicago, Chicago, IL; [5]Wake Forest U, Winston-Salem, NC; [6]UAB, Birmingham, AL; [7]OMRF, Oklahoma City, OK; [8]Wash Hosp Ctr, Washington, DC; [9]U Michigan, Ann Arbor, MI; [10]Human Genome Sciences, Rockville, MD

Presentation Number: 922

Poster Board Number: 317

Purpose: LymphoStat-B is a fully human monoclonal antibody (mAb), which inhibits soluble B-Lymphocyte Stimulator (BLyS). A randomized double-blind study evaluated the safety, tolerability, immunogenicity and pharmacology (PK) of 4 different doses (1, 4, 10, 20 mg/kg) of LymphoStat-B or placebo administered as a single IV infusion or 2 infusions 21 days apart. Subjects had stable mild to moderate SLE disease activity and were on a stable standard of care SLE treatment regimen for 2 months prior to enrollment.

Methods: Patients were followed for 84-105 days for assessment of adverse events (AEs), PK and safety plus measurement of peripheral B-cell concentrations, serologies and disease activity (SELENA SLEDAI). Data from placebo subjects (n=13) in single or double dose cohorts were pooled and compared to LymphoStat-B subjects (n=57) in each of the 4 single or double dose cohorts.

Results: Study subjects were predominantly female (91%) with an average age of 41. The mean disease duration was 8.5 years with a baseline mean SELENA SLEDAI score = 2.2. LymphoStat-B was well tolerated at all doses with no study withdrawals. The overall incidence of AEs was similar between LymphoStat-B and placebo groups. There was no increased incidence of infections in the treatment group, and none of the infections reported were attributed to study agent. Six patients experienced serious adverse events with similar frequencies observed in the placebo and treatment groups. None were deemed related to study agent. Severe (grade 3 and 4) laboratory abnormalities or AEs occurred infrequently. One patient experienced an infusion reaction at the highest single dose. One patient developed neutralizing antibodies to LymphoStat-B. Pharmacokinetics of single doses were dose-proportional. Long $t_{1/2}$ = 13-17 days, slow clearance = 4.00 ± 1.56 mL/day/kg and small Vss = 68.19 ± 20.83 mL/kg are consistent with a fully human mAb. All LymphoStat-B cohorts had significant reductions of $CD20^+$ cells (12-47%) at 1 or more visits from day 42-105 compared to placebo. Reductions in anti-dsDNA or Ig levels were observed in some LymphoStat-B cohorts compared to placebo. No change in SLE disease activity was observed over this short exposure.

Conclusions: LymphoStat-B was well tolerated in SLE patients. There was a significant reduction of peripheral B-cells by LymphoStat-B consistent with its ability to bind and inhibit the biological activity of BLyS. These results support phase II trials testing for clinical benefit in patients with SLE and other autoimmune diseases.